Title page

Title: Comparison of transcatheter to surgical aortic valve implantation in high risk patients: A nationwide study in France.

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Glossary of Abbreviations:

AHA/ACC: American Heart Association/American College of cardiology

AVR: Aortic valve replacement

DRG: Diagnosis-Related-Group

ESC: European Society of Cardiology

GEE: Generalized Estimating Equations

HR: Hazard ratio

ICD: International Classification of Diseases

PMSI: French Medical Information System

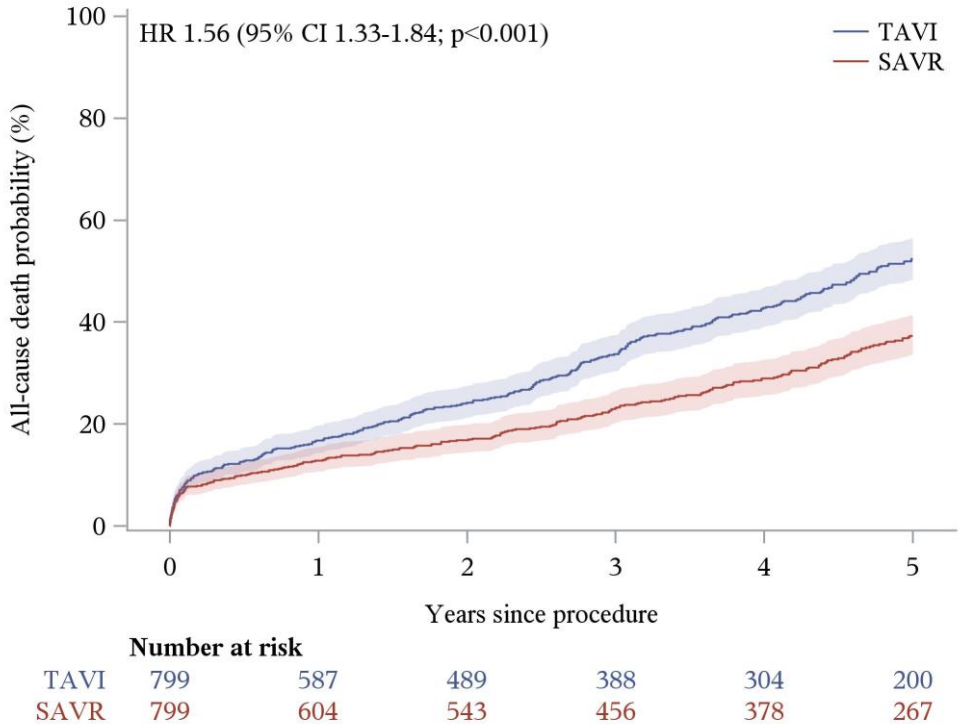
PSM: Propensity-score matching

RCT: Randomised controlled trial

SAVR: Surgical aortic valve replacement

TAVI: Transcatheter aortic valve implantation

Central picture



Legend: Cumulative probability of all-cause in-hospital mortality

Time varying outcome with shaded areas showing 95% confidence intervals based on 1-Kaplan-Meier estimation of TAVI (transcatheter aortic valve implantation) vs. SAVR (surgical aortic valve replacement); HR = Hazard ratio.

Central message

In patients with high-surgical risk, our study using real-world evidence shows TAVI to be associated with a greater risk of mortality after 1 year which is sustained up to 5 years

Perspective statement

The extension of TAVI indications in patients other than those with high or prohibitive-surgical risk should be cautious until further data, either based on RCTs or real-world evidence, are made available to inform on the relative long-term effectiveness of TAVI compared to SAVR.

Structured Abstract (241 words)

Objective: To compare the clinical outcomes and direct costs at 5 years between TAVI or SAVR using real-world evidence.

Methods: We performed a nationwide longitudinal study using data from the French Hospital Information System over 2009-2015. We matched inside hospitals two cohorts of adults who underwent TAVI or SAVR in 2010 on propensity score based on patients characteristics. Outcomes analysis included mortality, morbidity, and total costs and with a maximum 60-month follow-up. Clinical outcomes were compared between cohorts using Hazard Ratios (HR) estimated from Cox proportional hazards model for all-cause death, and from Fine and Gray's competing risk model for morbidity.

Results: Based on a cohort of 1598 patients (799 in each group) from 27 centers, a higher risk of death was observed after 1 year with TAVI compared to SAVR (16.8% vs. 12.8% respectively; HR 1.33, 95%CI 1.02-1.72) and was sustained up to 5 years (52.4% vs. 37.2%; HR 1.56, 95%CI 1.33-1.84). At 5 years, the risk of stroke was increased (HR 1.64, 95%CI 1.07-2.54) as was myocardial infarction (HR 2.30, 95%CI 1.12-4.69) and pacemaker implantation (HR 2.40, 95%CI 1.81-3.17) after TAVI. The hospitalization costs per patient at 5 years were €69,083 after TAVI and €55,687 after SAVR ($p<0.001$).

Conclusions: In our study, high-risk patients after TAVI harbor a greater risk of mortality and morbidity at 5 years compared to SAVR and higher hospitalizations costs. Those results should encourage to be more cautious before enlarging the indications of TAVI.

Introduction

More than 15 years after the first-in-man case,[1] transcatheter aortic valve implantation (TAVI) continues to revolutionize the management of severe aortic stenosis and has become over time a routinely performed procedure in many cardiac centers worldwide. In early 2014, more than 100,000 had been performed.[2] While the benefit of TAVI was initially demonstrated in patients ineligible or at high-surgical risk,[3, 4] a growing number of studies have evaluated TAVI in patients with low-to-intermediate risk.[5, 6] This has contributed to the currently observed trend toward enlarged indications of TAVI in patients that would otherwise undergo surgical aortic valve replacement (SAVR). Several randomised controlled trial (RCTs) conducted among carefully selected populations have shown promising results on the clinical effectiveness and safety of TAVI compared to surgery.[4, 5, 7] Conversely, evidence from real-world data indicate a better outcome with surgery compared to TAVI.[8] Overall, the largest reported cohorts have a follow-up limited to one to three years in maximum[9, 10] which is insufficient to provide a long-term view after aortic valve replacement (AVR).

This nationwide study aimed to compare the long-term clinical outcomes and costs between patients undergoing TAVI and SAVR.

Material and Methods

Study design and participants

We conducted a propensity-matched cohort study based on the French Medical Information System (*programme de médicalisation des systèmes d'information [PMSI]*). The PMSI is a large hospital database with prospectively collected data from all public and private hospitals in France. The database is routinely implemented for the purpose of care reimbursement leading to very strong accuracy and exhaustive collection of the data. As a consequence no patients were lost to follow-up during the considered period. Moreover, the PMSI has a

system of coding with strict variable definitions and a subset of records audited on a regular basis in order to avoid an excessive high rates of coding errors. Inpatient's stays are converted into one Diagnosis-Related-Group (DRG) based on standard discharge abstracts containing compulsory information about the patient, primary and secondary diagnoses, using the International Classification of Diseases (10th revision - ICD-10), as well as procedural codes associated with the care provided.

We selected all adults who underwent TAVI or SAVR in French institutions between 1, January, 2010 and 31, December, 2010. In order to homogenize study population, we only selected cases with a main diagnosis of heart failure, rheumatic or nonrheumatic aortic valve disease (ICD-10 codes I06*, I35*, or I50*). Patients <18 years, having experienced ambulatory care, or with data inaccuracies were not retained in final cohorts. Within the index hospitalization stay, we extracted patients' demographics and socioeconomic characteristics, co-morbidities according to Charlson and/or Elixhauser algorithms[11], the type and emergency context of surgical procedure, and length of stay. We subsequently used patient unique anonymous number in order to link his/her stays in acute and rehabilitation care, allowing the extraction of hospitalization-related data from 12 months preceding TAVI and SAVR to a maximum of 60 months thereafter.

Outcomes

The primary endpoint was in-hospital mortality from the index hospitalization up to five years following TAVI or SAVR. Other outcomes included the occurrence of postoperative admission in intensive (≥2 nights) or critical care unit (≥5 nights), reoperation, stroke, myocardial infarction, or pacemaker implantation.

Economic evaluation was performed from the hospital perspective based on the total number of hospitalization stays, days, and costs over 5 years in acute or rehabilitation care. We valued

in Euros (€) the in-hospital medical resources consumptions using average expenditures as observed in the national cost scale for the medicine, surgery, and obstetrics sector.

Statistical analysis

To control for the nonrandom assignment of patients to one of the two procedures, we formed matched pairs of TAVI and SAVR patients using propensity scores. First, propensity scores were estimated as the predicted probability of a patient undergoing TAVI using a logistic regression model including the following covariates: sex, age (continuous, with linear, quadratic and cubic terms), household income (continuous), number of days spent in acute care hospitalizations the year before the index stay (continuous, with linear, quadratic and cubic terms), emergency procedure, and a selection of comorbidities (i.e. congestive heart failure, cardiac arrhythmia, pulmonary circulation disorder, peripheral vascular disease, hypertension, chronic pulmonary disease, diabetes, renal disease, liver disease, obesity, myocardial infarction, and cerebrovascular disease). We then matched patients with the closest propensity score inside hospital to control for confounders at hospital level, using a greedy 1:1 algorithm without replacement and requiring that the logit of the propensity score of a patient who underwent TAVI and one who underwent SAVR be within 0·20 standard deviations of one another. Standardized differences were used to assess the degree of balance between the matched groups for baseline characteristics. An absolute standardized difference of $\leq$0·10 was chosen to indicate a negligible difference in the mean or prevalence of a variable between groups. Balance for continuous variables was also assessed with graphical methods (side-by-side boxplots, empirical cumulative distribution functions, empirical QQ-plots) to compare the distributions across the two groups. Sensitivity analysis was conducted for the main outcomes (all-cause death and costs) with 1:1 nearest neighbor matching with replacement within caliper of 0.20 standard deviation of the logit of the propensity score, with

the inclusion of weights in the outcome models (TAVI patients were weighted at 1 and the weight for a SAVR patient was the number of times it was matched to a TAVI patient).

Categorical variables were presented using absolute and relative frequencies and continuous variables were presented using medians and interquartile ranges. Estimates were accompanied with the corresponding 95% CI and p-values of less than 0.05 were considered to indicate statistical significance.

Clinical outcomes were assessed as time-to-event variables, and were evaluated at different time points *t* (1 month, 6 months, then yearly up to 5 years after index procedure). Cumulative probabilities of events over time were estimated with the non-parametric 1-Kaplan-Meier estimator for all-cause death, and with the non-parametric Cumulative Incidence Functions estimator using competing risk of death for postoperative stay in intensive or critical care unit, reoperation, stroke, myocardial infarction, and pacemaker. To compare the effect of procedure (TAVI vs. SAVR), Hazard Ratios (HR) were estimated between time 0 and time *t*, from Cox proportional hazards model for all-cause death, and from Fine and Gray's model using competing risk of death for other clinical outcomes, with robust variance estimator to account for clustering within matched pairs. A sensitivity analysis was performed for the main clinical outcome (all-cause death) with a nested frailty model to take into account the two hierarchical levels of clustering (matched pairs nested within hospitals).

Health care utilization (number of hospitalization stays, days, and costs) were assessed as count variables, and were evaluated at different time points *t*. The rate of health care utilization per patient-year was the total number of health care utilization in each procedure group divided by the total follow-up duration (date of the procedure until the date of death or

end of the study period) of all patients in that group between time 0 and time *t*. The consequent rate ratio (RR) comparing TAVI to SAVR was estimated using Generalized Estimating Equations (GEE) with a log link, a Poisson distribution, and the log of the follow-up time as an offset. Robust standard errors were estimated using an independent or exchangeable working correlation structure and clustering on matched-pairs to account for over dispersion (dependency within matched pairs and within patients experiencing repeated events). A sensitivity analysis was performed for the main economic outcome (costs) with a multilevel Poisson regression model to take into account the two hierarchical levels of clustering (matched pairs nested within hospitals). Mean cumulative numbers of health care utilization per person at time *t* were estimated by multiplying the predicted rate by *t*. Sensitivity analyses were performed with a Negative Binomial distribution for all economic outcomes and with a Gamma distribution for costs, providing rate ratio estimations.

Data manipulation and analyses were performed using SAS (version 9·4; SAS Institute Inc., Cary, NC) and R (version 3.3.2; R Core Team) softwares.

Ethics approval:

This study was strictly observational and we used anonymous data retrospectively. Therefore, in accordance to the French regulation on "non-interventional clinical research", the written informed consent from the participants or the authorization from an ethical committee was not required.

Results

Participants/descriptive data

During Year 2010, 1334 patients underwent TAVI and 6,695 patients underwent SAVR at 27 French hospitals. After applying the selection and matching criteria, 799 pairs of patients were retained in final analysis (Supplemental 1). Cohorts' baseline characteristics are listed in Table 1 with negligible difference between those (evolution pre and post-matching is presented in the Supplemental 2), and distribution of the propensity scores pre and post-matching are represented in the Supplemental 5.

Short-term clinical outcomes

The risk of hospital death from any cause at 30 days, 6 months, and 1 year was respectively 7.5%, 12.7%, and 16.8% in the TAVI group, and 6.6%, 10.0%, and 12.8% in the SAVR group, and was not different between both groups at 30 days and 6 months (respectively HR 1.15, 95%CI 0.79-1.68; 1.29, 95%CI 0.96-1.73) but was higher after TAVI at 1 year (HR 1.33, 95%CI 1.02-1.72).

At 1 year, there was no significant difference in the occurrence of reoperation (1.9% with TAVI vs. 0.9% with SAVR) or myocardial infarction (0.6% with TAVI vs. 0.1% with SAVR), but the risk of stroke was higher after TAVI (2.4% vs. 0.9% respectively; HR 2.73, 95%CI 1.14-6.53) as was the risk of new pacemaker implantation (14.5% vs. 4.9% respectively; HR 3.19, 95%CI 2.23-4.56).

Long-term clinical outcomes

The cumulative probabilities and HR of each clinical outcome from 1 to 5 years are presented in Table 2, accompanied with the cumulative probability curves for death (Central figure) and for the other clinical outcomes (Supplemental 6).

A higher risk of death was observed 2 years after TAVI compared to SAVR (24.2% vs. 16.8% respectively; HR 1.47, 95%CI 1.17-1.84) and sustained up to 5 years (52.4% vs. 37.3% respectively; HR 1.56, 95%CI 1.33-1.84).

At 5 years, there was a trend toward a higher risk of reoperation after TAVI compared to SAVR (2.3% vs. 1.1%: HR 2.01, 95%CI 0.90-4.50), while the risk of stroke significantly increased (6.9% vs. 4.3% respectively; HR 1.64, 95%CI 1.07-2.54), as was myocardial infarction (3.1% vs. 1.4% respectively; HR 2.30, 95%CI 1.12-4.69), or new pacemaker implantation (20.4% vs. 9.3% respectively; HR 2.40, 95%CI 1.81-3.17).

Hospitalization data and cost evaluation

Hospitalization data and cost evaluation up to 5 years after the procedure are presented in Table 3 and figure 1. At 1 year, the mean cumulative hospitalization costs per patient were €42,238 after TAVI and €35,128 after SAVR (RR 1.20, 95%CI 1.13-1.28). The increased cost with TAVI was mainly attributed to the procedure performed during the index stay and was sustained up to 5 years (€69,083 vs. €55,687 respectively; RR 1.24, 95%CI 1.13-1.36). The mean cumulative numbers of hospitalization stays and of days of hospitalization per patient were similar at any time in both groups, except for the mean cumulative number of days of hospitalization at 1 year which was lower after TAVI (RR 0.86, 95%CI 0.79-0.94).

Sensitivity analysis for the main outcomes

Matching with replacement resulted in 1089 matched-pairs of TAVI and SAVR and the same trends for all-cause death and costs, although effects were attenuated and results at 1 year up to 3 years became non-significant (Supplemental 7).

In the cohort matched without replacement, the nested frailty model for all-cause death resulted in very similar effects (Supplemental 8), whereas the multilevel Poisson regression for costs did not converge.

Discussion

Principal findings

We have used real-world data from a nationwide database including 100% of the cases during the considered period to compare the long-term clinical outcomes between TAVI and SAVR in two propensity score matched cohorts of patients. Our findings showed an increased risk of death after TAVI at 1 year that increased up to 50% at 5 years. There were also a much higher risk of stroke, myocardial infarction and pacemaker implantation after TAVI with higher cumulated costs relating with the index hospitalisation stay.

Comparison with other studies

The entire TAVI population (n=1274) that we identified from the database was also part of the *France 2* French registry that enrolled 3195 high-risk patients (mean Logistic Euroscore 21% / 74% with a Logistic Euroscore ≥ 20%) between January 2010 and October 2011.[3] While the entire SAVR population had a lower risk compared to the entire TAVI population, we selected a cohort of patients with much higher risk profile within the entire SAVR population. Hence, we assume that matching between these populations allowed us to compare similar cohorts of high-risk patients.

Our survival estimates are supported by a longer follow up and larger study sample than previous publications comparing the two procedures (Table 4). Among RCTs that included high-risk patients (Logistic Euroscore 18%-29%), there was no significant difference on the

298 risk of death at three years[12] and five years.[13] The results from our study in high-risk patients
299 contrast greatly with those reported in these two RCTs. While our study outcomes after TAVI
300 were comparable to those in the US COREVALVE RCT, the survival after SAVR was far
301 better compared to US COREVALVE. Among the four published propensity-score
302 matching (PSM) cohort analyses that selected high-risk patients, two studies[10, 14] showed no
303 difference in mortality after 1 year while two other studies reported a greater mortality with
304 TAVI from the first year and up to two[15] or four [16] years of follow-up. This increase in
305 mortality with TAVI compared to SAVR is consistent with our findings and has been recently
306 emphasized in a meta-analysis of studies that used PSM.[8]
307 The magnitude of the mortality-increase after TAVI compared to SAVR raises the question
308 on the comparability of TAVI and SAVR cohorts matched using PSM and will be further
309 discussed. However, we believe that the systematic presence of unidentified confounders
310 within healthcare databases used across different country settings is unlikely.
311
312 Although our study did only include high-risk patients, we also examined the published
313 outcomes after TAVI or SAVR in people with intermediate-risk patients (Table 4) owing to
314 the increase used of TAVI in this population.
315 Three RCTs that included people with a lower surgical risk reported a similar risk of mortality
316 but to date the follow-up is limited to a maximum of two-years.[5, 17-19] Two other studies using
317 PSM in people with similar risk-profile showed a higher risk of death after TAVI at 3 years. [9]
318 [20] Conversely, Thourani et al.[21] reported a reduced mortality after TAVI at 1 year but these
319 latter results are however subject to caution given the presence of several major
320 methodological flaws pertaining to the covariates that were included in the propensity score
321 model.[22]
322

We have observed an increased risk of stroke at five years with TAVI compared to SAVR. We cannot provide interpretation of these findings based on data pertaining to onset of post-procedural atrial fibrillation or use of anticoagulation regimen at follow-up. One might speculate that TAVI patients mostly received dual antiplatelet therapy with clopidogrel and aspirin while SAVR patients received mostly VKA or just aspirin for three months. However, in the absence of formal recommendations on anticoagulation management, we believe there are lots of variations across centers.

Our study provides further information on hospital resource consumption between TAVI and SAVR. The cumulative costs were higher after TAVI while there were no differences at 5 years regarding the number of stays or days consumed at hospital. Furthermore, the lower number of hospitalisations contrasts with the higher total costs at 1 year post-TAVI compared to SAVR, which can be explained by the cost of TAVI device during the index stay. Although our study was not designed as a cost-effectiveness evaluation, our results showing a reduced survival and higher costs with TAVI suggest that TAVI would be dominated by SAVR.

Limitations

Our study carries several limitations. We identified two cohorts of patients from the French PMSI database, which is increasingly used in health service research given the exhaustive collection of medical information at the whole country population. [23, 24] To control for the non-random assignment of patients between TAVI and SAVR procedures, we used propensity-score-matching-adjustment based on a high number of patient characteristics and with control for confounders at hospital level. The risk of bias with PSM studies is to omit some potential confounders that can alter the comparability of populations and therefore threaten the validity of outcome measures.[25] The PMSI database does not enable to precisely

calculate the Euroscore because the clinical variables that are available are not strictly those listed or are not as accurately defined among the factors that are accounted for in the Euroscore calculation. Because data granularity did not allow us to accurately describe every patients profile with respect to the surgical risk, we added the number of hospitalization days in acute care consumed the year preceding the index stay to account for unmeasured confounders. Among variables available within the PMSI database, we chose in our propensity-score based method those with the most clinical relevance to discriminate the mortality/morbidity risk of populations but also accounting for those with a sufficient degree of validity. We are aware that the PMSI database variables may also lack of granularity to account for factors such as patient frailty or the complexity of the procedure.

A weakness of large hospital databases is the miscoding of diagnoses during hospital stays that can underestimate patient's comorbidities.[26] This issue is not specific to a disease area or to certain type of procedure and is more influenced by a strong coding variability between healthcare providers and across years. Given this, we matched pairs of patients who underwent either TAVI or SAVR inside the same hospital and over the same period. Hence, we believe there is no a priori reason that miscoding would be more prominent in one cohort than another and would alter their comparability. Another limitation relates to our inability to capture deaths occurring outside hospital, which means that the mortality rates might be slightly underestimated. However the rate of death occurring outside hospitals is today extremely rare and probably negligible. There might also have been an underreporting of adverse events as suggested by the low incidence of stroke, myocardial infarction, or permanent pacemaker implantation observed in this study. Again, this issue is not specific to certain procedure type and we assume that the relative occurrence of these events between TAVI and SAVI was adequately estimated. Finally, the selected cohorts were treated during Year 2010, that is seven years ago, and may therefore be less representative of contemporary

practices and outcomes related to TAVI in French centers since patients characteristics, devices, and experience of centers have surely evolved in recent years. However, this choice enabled to provide the longest ever reported follow-up of TAVI patients based on real-world data.

Practical implications

The 2017 guidelines from the European Society of Cardiology (ESC)[27] have considered TAVI in patients who are suitable for SAVR as assessed by the Heart Team but also an alternative to surgery in people who are at increased surgical risk, the decision being made by the heart team according to each patient characteristics. Accounting for the results of the Partner 2 trial,[5] the AHA/ACC recently updated guidelines have extended the indication of TAVI to intermediate surgical risk depending on patient-specific procedural risks, values, and preferences.[28] Based on these updated guidelines, the trend toward an enlarged use of TAVI to lower surgical risk patients is likely to get amplified to a great extent. As previously emphasized, the results from Partner 2 that suggest the non-inferiority of TAVI and SAVR in intermediate-risk patients are only available at two years which is notably insufficient to evaluate the long-term effectiveness of TAVI compared to SAVR for which the outcomes is demonstrated beyond twenty years. Moreover, the results from Partner 2[5], along with those of Partner-high risk[13], may be not representative of real-world clinical outcomes. Our results showed an increased risk of mortality for TAVI compared to SAVR using a large nationwide database providing real-word evidence over a long-term perspective. The implication of our findings is that the extension of TAVI in patients other than those with high or prohibitive-surgical risk should be cautious until further data, either based on RCTs or real-world evidence, are made available to inform on the relative long-term effectiveness of TAVI compared to SAVR.

Conclusions

Our study showed that patients after TAVI, compared to those who underwent SAVR, harbor a greater risk of mortality and morbidity at 5 years, and had higher costs of hospitalizations. These results indicate that more data are needed before considering an enlargement of TAVI indications in people eligible to conventional surgery.

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Figure legend:

Figure 1: Mean Cumulative costs over time

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement.

Predictions from GEE Poisson regression model.

Supplementary material

Supplementary material 1: Study flowchart

Supplementary material 2: Baseline characteristics of patients before and after matching

Supplementary material 3: Cumulative probability of all-cause in-hospital mortality

Supplementary material 4: Mean cumulative costs per person

Supplementary material 5 – Propensity scores distribution before (left) and after (right) matching

Supplementary material 6 – Cumulative incidence curves (cumulative probability of events)

Supplementary material 7 - Sensitivity analysis (Matching with replacement)

Supplementary material 8 - Sensitivity analysis (Multilevel modelling for the outcomes)

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Table 1- Baseline characteristics of patients post-matching

	TAVI (n=799)	SAVR (n=799)	Standardized differences
Male sex	427 (53.4%)	434 (54.3%)	-0.018
Age, years	81 [76 – 85]	81 [77 – 85]	0.002
Income, euros	19659 [18285 – 21971]	19734 [18395 – 22073]	-0.060
Days of hospitalization in the previous year	11 [4 – 23]	10 [4 – 24]	-0.006
Emergency procedure	13 (1.6%)	13 (1.6%)	0.000
Congestive heart failure	284 (35.5%)	278 (34.8%)	0.016
Cardiac arrhythmias	420 (52.6%)	427 (53.4%)	-0.018
Pulmonary circulation disorders	63 (7.9%)	76 (9.5%)	-0.058
Peripheral vascular disease	90 (11.3%)	93 (11.6%)	-0.012
Hypertension	350 (43.8%)	338 (42.3%)	0.030
Chronic pulmonary disease	89 (11.1%)	88 (11.0%)	0.004
Diabetes	155 (19.4%)	176 (22.0%)	-0.065
Renal disease	122 (15.3%)	119 (14.9%)	0.010
Liver disease	23 (2.9%)	21 (2.6%)	0.015
Obesity	71 (8.9%)	62 (7.8%)	0.041
Myocardial infarction	52 (6.5%)	44 (5.5%)	0.042
Cerebrovascular disease	69 (8.6%)	79 (9.9%)	-0.043

Values are number (%) or median [interquartile range].

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement.

Table 2- Compared clinical outcomes between TAVI and SAVR cohorts

Time t	TAVI (n=799)		SAVR (n=799)		HR[b] [CI 95%]	p-value[b]
	N events	% [95% CI][a]	N events	% [95% CI][a]		
All-cause death						
At 1 year	127	16.8 [14.3 ─ 19.6]	97	12.8 [10.6 ─ 15.4]	1.33 [1.02 ─ 1.72]	0.033
At 2 years	177	24.2 [21.2 ─ 27.5]	124	16.8 [14.3 ─ 19.7]	1.47 [1.17 ─ 1.84]	0.001
At 3 years	235	33.7 [30.3 ─ 37.4]	163	23.1 [20.1 ─ 26.4]	1.52 [1.25 ─ 1.85]	<0.001
At 4 years	286	42.8 [39.0 ─ 46.7]	196	29.0 [25.6 ─ 32.6]	1.58 [1.32 ─ 1.89]	<0.001
At 5 years	332	52.4 [48.4 ─ 56.5]	236	37.3 [33.5 ─ 41.4]	1.56 [1.33 ─ 1.84]	<0.001
Postoperative stay in ICU/CCU						
At 1 year	296	37.0 [33.7 ─ 40.4]	537	67.2 [63.8 ─ 70.3]	0.48 [0.43 ─ 0.55]	<0.001
At 2 years	313	39.2 [35.8 ─ 42.5]	540	67.6 [64.2 ─ 70.7]	0.50 [0.45 ─ 0.57]	<0.001
At 3 years	326	40.8 [37.4 ─ 44.2]	548	68.6 [65.2 ─ 71.7]	0.51 [0.46 ─ 0.57]	<0.001
At 4 years	334	41.8 [38.4 ─ 45.2]	550	68.8 [65.5 ─ 71.9]	0.52 [0.46 ─ 0.58]	<0.001
At 5 years	340	42.6 [39.1 ─ 45.9]	556	69.6 [66.3 ─ 72.6]	0.52 [0.46 ─ 0.58]	<0.001
Reoperation						
At 1 year	15	1.9 [1.1 ─ 3.0]	7	0.9 [0.4 ─ 1.7]	2.15 [0.87 ─ 5.30]	0.097
At 2 years	16	2.0 [1.2 ─ 3.2]	7	0.9 [0.4 ─ 1.7]	2.29 [0.94 ─ 5.60]	0.069
At 3 years	16	2.0 [1.2 ─ 3.2]	8	1.0 [0.5 ─ 1.9]	2.01 [0.85 ─ 4.71]	0.110
At 4 years	17	2.1 [1.3 ─ 3.3]	9	1.1 [0.6 ─ 2.1]	1.90 [0.84 ─ 4.28]	0.123
At 5 years	18	2.3 [1.4 ─ 3.5]	9	1.1 [0.6 ─ 2.1]	2.01 [0.90 ─ 4.50]	0.090
Stroke						
At 1 year	19	2.4 [1.5 ─ 3.6]	7	0.9 [0.4 ─ 1.7]	2.73 [1.14 ─ 6.53]	0.024
At 2 years	26	3.3 [2.2 ─ 4.7]	16	2.0 [1.2 ─ 3.2]	1.64 [0.87 ─ 3.08]	0.124
At 3 years	40	5.0 [3.6 ─ 6.7]	23	2.9 [1.9 ─ 4.2]	1.76 [1.05 ─ 2.94]	0.031
At 4 years	47	5.9 [4.4 ─ 7.7]	27	3.4 [2.3 ─ 4.8]	1.76 [1.10 ─ 2.84]	0.020
At 5 years	55	6.9 [5.3 ─ 8.8]	34	4.3 [3.0 ─ 5.8]	1.64 [1.07 ─ 2.54]	0.025
Myocardial infarction						
At 1 year	5	0.6 [0.2 ─ 1.4]	1	0.1 [0.0 ─ 0.7]	5.01 [0.58 ─ 42.94]	0.142
At 2 years	13	1.6 [0.9 ─ 2.7]	4	0.5 [0.2 ─ 1.2]	3.27 [1.06 ─ 10.06]	0.039
At 3 years	17	2.1 [1.3 ─ 3.3]	6	0.8 [0.3 ─ 1.6]	2.86 [1.12 ─ 7.27]	0.028
At 4 years	19	2.4 [1.5 ─ 3.6]	8	1.0 [0.5 ─ 1.9]	2.39 [1.04 ─ 5.50]	0.039
At 5 years	25	3.1 [2.1 ─ 4.5]	11	1.4 [0.7 ─ 2.4]	2.30 [1.12 ─ 4.69]	0.023
Pacemaker						
At 1 year	116	14.5 [12.2 ─ 17.1]	39	4.9 [3.5 ─ 6.5]	3.19 [2.23 ─ 4.56]	<0.001

At 2 years	125	15.6 [13.2 ─ 18.3]	48	6.0 [4.5 ─ 7.8]	2.80 [2.01 ─ 3.91]	<0.001
At 3 years	137	17.1 [14.6 ─ 19.8]	60	7.5 [5.8 ─ 9.5]	2.47 [1.82 ─ 3.35]	<0.001
At 4 years	156	19.5 [16.9 ─ 22.3]	70	8.8 [6.9 ─ 10.9]	2.42 [1.82 ─ 3.22]	<0.001
At 5 years	163	20.4 [17.7 ─ 23.3]	74	9.3 [7.4 ─ 11.4]	2.40 [1.81 ─ 3.17]	<0.001

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement

a Cumulative probability of event [95% CI] at time t from the nonparametric (1- Kaplan-Meier) estimator for all-cause death; and from the nonparametric Cumulative Incidence Functions estimator using competing risk of death for the other outcomes.

b Hazard Ratios (instantaneous rate of event for TAVI relative to SAVR at any time t) [95% CI] and p-value, estimated between time 0 and time t, from Cox proportional hazards model for all-cause death; and from Fine and Gray's competing risk model for the other outcomes. Matched-pairs design was taken into account with robust variance estimator.

Table 3- Compared health care utilization outcomes between TAVI and SAVR cohorts

Time t	TAVI (n=799)			SAVR (n=799)			Rate Ratio [95% CI] [a]	p-value[a]
	Total number of health care utilization	Total follow-up (PY)	Mean cumulative number per person[a]	Total number of health care utilization	Total follow-up (PY)	Mean cumulative number per person[a]		
Number of hospitalization stays								
At 1 year	3184	703.61	4.51	3719	724.11	5.10	0.88 [0.72 ─ 1.09]	0.255
At 2 years	4374	1349.18	6.46	5478	1411.32	7.71	0.84 [0.64 ─ 1.10]	0.200
At 3 years	5526	1946.03	8.50	7222	2069.87	10.42	0.82 [0.60 ─ 1.11]	0.192
At 4 years	6843	2480.04	11.02	8641	2689.18	12.81	0.86 [0.61 ─ 1.20]	0.381
At 5 years	7769	2969.54	13.07	10097	3272.01	15.39	0.85 [0.60 ─ 1.21]	0.368
Number of days of hospitalization								
At 1 year	35809	703.61	50.04	43040	724.11	58.16	0.86 [0.79 ─ 0.94]	0.001
At 2 years	45028	1349.18	65.05	51836	1411.32	71.20	0.91 [0.83 ─ 1.01]	0.071
At 3 years	53527	1946.03	80.36	61474	2069.87	86.17	0.93 [0.84 ─ 1.03]	0.177
At 4 years	61887	2480.04	97.23	70014	2689.18	100.72	0.97 [0.87 ─ 1.07]	0.514
At 5 years	68434	2969.54	112.02	79378	3272.01	116.93	0.96 [0.86 ─ 1.07]	0.432
Costs								
At 1 year	30774212	703.61	42238	26604033	724.11	35128	1.20 [1.13 ─ 1.28]	<0.001
At 2 years	35123650	1349.18	49330	30183988	1411.32	39917	1.24 [1.15 ─ 1.33]	<0.001
At 3 years	39051054	1946.03	56102	34014554	2069.87	45031	1.25 [1.15 ─ 1.35]	<0.001
At 4 years	42295035	2480.04	62992	37295324	2689.18	50107	1.26 [1.15 ─ 1.37]	<0.001
At 5 years	44889719	2969.54	69083	40860170	3272.01	55687	1.24 [1.13 ─ 1.36]	<0.001

TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement; PY=Person-year.[a]From GEE Poisson regression model.

Table 4- Summary of studies identified in our literature search

Author/study name	Inclusion period	Country	Centers	Sample size	Method of comparison	STS (%)	Logistic Euroscore I (%)	All cause death									
								1 year		2 years		3 years		4 years		5 years	
								TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR	TAVI	SAVR
High-risk patients																	
Partner 1 [13, 29, 30]	2007-2009	>USA	25	348/351	RCT	11.8/11.7	29.3/29.2	24.2%	26.8% p=0.44	33.9%	35.0% p=0.78	/		/		67.8%	62.4% p=0.76
US Corevalve [7, 12, 31]	2011-2012	USA	45	391/359		7.3/7.5	17.6/18.4	14.2%	19.1% p=0.04	22.2%	28.6% p=0.04	32.9%	39.1% p=0.068	/		/	
Latib et al. [14]	2003–2008 + 2007–2011	Italy	1	111/111	PSM	4.6/4.6	23.2/24.4	6.4%	8.1% p=0.80	/		/		/		/	
Piazza et al.[10]	2006-2010	3 in EU	3	405/405		/	17.1/17.5	17.5%	16.5%** * p=0.93	/		/		/		/	
Johansson et al. [16]	1999-2014	Sweden	1	166/125		/	23/20	19.5%	10.4% p=0.001	/		/		48.2%	27.% p=0.001	/	
Muneretto et al. [15]	2007-2014	EU	7	204/204		8.2/8.4	19.5/19.2	9.9%	3.3% p<0.001	20.5%	8.7% p<0.001	/		/		/	
Our study	2010	France	27 (nationwide)	832/832		/	/	15.7%	13.8% p=0.326	22.8%	17.4% p=0.021	32.5%	22.3% p<0.001	42.0%	29.5% p<0.001	51.5%	36.2% p<0.001

Intermediate-risk patients												
Notion [17 18]	2009-2013	Denmark	3	145/135	RCT	2.9/3.1	8.4/8.9	4.9% 7.5% p=0.38	8.0% 9.8% p=0.54	/	/	/
Partner 2[5]	2011-2013	USA	57	1011/1021		5.8/5.8	/	12.3% 12.9% p=0.69	16.7% 18.0% p=0.45	/	/	/
Surtavi[19]	2012-2016	USA, Europe, Canada	87	879/867		4.4/4.5	11.9/11.6	6.7% 6.8% NS	12.6% 14.0% NS	/	/	/
Schymik et al.[9]	2007-2012	Germany	1	216/216	PSM	/	8.7/8.8	11.6% 7.4% p=0.157*	17.1% 9.7% p=0.157*	19.9% 14.3% p=0.157*	/	/
Rosato et al.[20]	2010-2012	Italy	93 (nationwide)	355/355		/	6.3/6.3	11.4% 7.8% p=0.0075*	19.6% 12.8% p=0.0075*	28.0% 16.6% p=0.0075*	/	/
Thourani et al.[21]	2011- 2013 + 2014	USA, Canada	51 + 57	1077/944	PSS	5.2/5.4	/	7.4% 13.0% p=0.0003	/	/	/	/

*TAVI = transcatheter aortic valve implantation; SAVR = surgical aortic valve replacement; RCT = randomized controlled trial; PSM = Propensity-Score Matching; PSS = Propensity-Score Stratification. * calculated over the 3 year period ** estimated from the number of deaths stated in the manuscript (71 in TAVI, 67 in SAVR)*